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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/816,081	04/01/2004	David B. Rozema	Mirus.035.02.1	8619
25032	7590	01/28/2008		
MIRUS CORPORATION 505 SOUTH ROSA RD MADISON, WI 53719			EXAMINER DUNSTON, JENNIFER ANN	
			ART UNIT	PAPER NUMBER
			1636	
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			01/28/2008	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/816,081	<b>Applicant(s)</b> ROZEMA ET AL.	
	<b>Examiner</b> Jennifer Dunston	<b>Art Unit</b> 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 31 August 2007 and 08 November 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 19,22,23 and 27-32 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 19,22,23 and 27-32 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 01 April 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/31/2007 has been entered.

Receipt is acknowledged of an amendment, filed 11/8/2007, in which the status identifier "previously presented" was provided for all pending claims. Currently, claims 19, 22, 23 and 27-32 are pending.

Applicant's request for reconsideration of the finality of the rejection of the last Office action is moot in view of the request for continued examination under 37 CFR 1.114. The response asserts that the new rejection of claim 19, in the Office action mailed 5/31/2007, was not necessitated by amendment, because claim 19 incorporated only limitations present in the originally filed claims. This is not found persuasive, because the amendment of claim 19 was not simply an incorporation of limitations of a single dependent claim. Rather, the amendment resulting in the incorporation of a combination of limitations taken from claim 21 and claim 26, resulting in a new combination of limitations not previously considered. For example, claim 21 required a negatively charged polymer, whereas the amended claim 19 required a polyamine polymer. The altered scope of the claim resulted in the withdrawal of numerous rejections under 35 USC §§102 and 103 and the presentation of new rejections under 35 USC § 103. The rejections were necessitated by amendment, and the action was properly made final.

***Election/Restrictions***

Applicant elected Group II without traverse in the reply filed on 9/18/2006. Currently, claims 19, 22, 23 and 27-32 are under consideration.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 23 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new rejection.

Claim 23 recites the limitation "said molecule" in line 23. There is insufficient antecedent basis for this limitation in the claim. It would be remedial to amend the claim to recite "said polynucleotide" in place of "said molecule."

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

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claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19, 22, 23 and 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff (WO 00/03694 A1, cited in a prior action; see the entire reference). This rejection was made in the Office action mailed 5/31/2007 and is reiterated below.

Wolff teaches a method for delivering a polynucleotide to the cytoplasm of a cell, comprising the steps of (i) condensing the polynucleotide with a cation to form a condensed polynucleotide binary complex (polycation/nucleic acid complex), (ii) associating the binary complex with a polyanion (polyanion/polycation/nucleic acid complex), and (iii) delivering the ternary complex to the cell where it is endocytosed (e.g., pages 16-19). Wolff teaches that the polyanion may be cleavable by the addition of a polyion cleavable in the side chain, where acids, esters and amides of carboxylic acid derivatives are reacted with amines (e.g., paragraph bridging pages 21-22). Specifically, Wolff teaches the reaction of dimethylmaleyl acid, a disubstituted maleic anhydride derivative, with an amine group on the polyion (e.g., paragraph bridging pages 11-12; paragraph bridging pages 21-22). Wolff teaches the reaction of the maleic anhydride derivative with the amine of the polymer to form a labile bond (e.g., paragraph bridging pages 21-22). The labile bond taught by Wolff et al is a pH-labile bond, as the specification teaches that the reaction of a maleic anhydride derivative with an amine results in the formation of a pH-labile bond (e.g., page 6, lines 14-15; Figure 2). Specific amines taught by

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Wolff et al are poly-L-lysine, spermine, spermidine, N,N'-bis(2-aminoethyl)-1,3-propanediamine (AEPD), and 3,3'-Diamino-N,N-dimethyldipropylammonium bromide (e.g., 6, lines 14-20; page 10, lines 13-19). Further, Wolff teaches that polyethylenimine (PEI, a polyamine) is capable of disrupting endosomal function without additional treatments. Moreover, Wolff teaches that agents that disrupt the endosome can be used to increase the delivery of the polynucleotide to certain parts of the cell (e.g., page 11, lines 18-21). Wolff teaches the formation of polymers containing two to more than 80 monomers, which would result in a molecular weight of at least 10,000 Daltons (e.g., paragraph bridging pages 6-7). Wolff teaches that the particles formed by the method are salt stable nanoparticles (e.g., Example 8; Table 3).

Wolff does not specifically teach the addition of dimethylmaleyl acid to polyethylenimine.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of delivering a polynucleotide of Wolff to include the modification of polyethylenimine with dimethylmaleyl acid because Wolff teaches the reaction of dimethylmaleyl acid with amino groups and Wolff teaches it is within the skill of the art to use polyethylenimine in transfection methods. The addition of dimethylmaleyl acid to the polyethylenimine would result in the formation of a negatively charged reversibly inhibited membrane active polymer, which results in the formation of a ternary complex with a net negative charge.

One would have been motivated to make such a modification in order to receive the expected benefit of increasing delivery to the cells through disruption of the endosome as taught by Wolff. Based upon the teachings of the cited references, the high skill of one of ordinary skill

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in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff (WO 00/03694 A1, cited in a prior action; see the entire reference) as applied to claims 19, 22, 23 and 29-32 above, and further in view of Wolff (WO 00/75164 A1, cited in a prior action; see the entire reference). This rejection was made in the Office action mailed 5/31/2007 and is reiterated below.

The teachings of Wolff (WO 00/03694) are described above and applied as before.

Wolff (WO 00/03694) does not teach the method where the disubstituted maleic anhydride derivative is carboxydimethylmaleic anhydride.

Wolff (WO 00/75164) teaches the synthesis of 2-propionic-3-methylmaleic anhydride (carboxydimethylmaleic anhydride or C-DM) and the reaction of this compound to polyamines for use in the transfection of cells with a polynucleotide (e.g., page 19, lines 20-25; page 21, line 15 to page 22, line 30; page 23, lines 21-25; page 63, lines 1-18; page 65, lines 8-14; page 66, lines 21-27; Example 7). Wolff teaches that the addition of 2,3-dimethylmaleamic acid to a polyamine increases the transfection efficiency as compared to succinimic modified polyamine (e.g., page 78, Table). Wolff teaches that 2-propionic-3-methylmaleamic modified polyamine further increases transcription efficiency as compared to 2,3-dimethylmaleamic acid under the same conditions (e.g. page 78, Table). Wolff teaches that the bond between the maleic acid anhydride derivative and the polyamine is a pH-labile bond, which would be cleaved in the

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endosome (e.g., paragraph bridging pages 20-21; paragraph bridging pages 22-23; page 24, lines 5-17).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the transfection method of Wolff (WO 00/03694) to replace the dimethylmaleyl acid with the carboxydimethylmaleic anhydride taught by Wolff (WO 00/75164) because both references teach it is within the ordinary skill in the art to react a maleic acid anhydride derivative with a polyamine for use in transfection of cells with a polynucleotide.

One would have been motivated to make such a modification in order to receive the expected benefit of increased transfection efficiency as taught by Wolff (WO 00/75164). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

### ***Response to Arguments - 35 USC § 103***

Applicant's arguments filed 8/31/2007 have been fully considered but they are not persuasive. The response essentially asserts that the references do not teach every limitation of the rejected claims. Specifically, the response asserts that Wolff does not teach any membrane active polymers or that membrane active polymers can be reversibly inhibited by maleic anhydride derivatives. This is not found persuasive. Wolff teaches PEI, a membrane active polymer. Wolff teaches the reaction of dimethylmaleyl acid, a disubstituted maleic anhydride derivative, with an amine group on a polyion (e.g., paragraph bridging pages 11-12; paragraph bridging pages 21-22). Wolff teaches the reaction of the maleic anhydride derivative with the



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amine of the polymer to form a labile bond (e.g., paragraph bridging pages 21-22). The labile bond taught by Wolff et al is a pH-labile bond. The present specification uses the term "reversibly inhibited" to mean a pH labile bond, which undergoes chemical cleavage in the acidic environment of the endosome (e.g., page 3, lines 11-14; page 9, lines 1-6). Thus, the teachings of Wolff render obvious a membrane active polymer reversibly inhibited by disubstituted maleic anhydride derivative. For these reasons, and the reasons made of record in the previous office actions, the rejections are maintained.

### *Conclusion*

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

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like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.  
Examiner  
Art Unit 1636

/JD/

/Daniel M. Sullivan/  
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Art Unit 1636